

**Remarks/Arguments:**

This Amendment accompanies a Request for Continued Examination. These remarks are responsive to the Final Office Action of December 10, 2008 and the Advisory Action of February 5, 2009. The rejections of claims 1 and 3 over Sharma under 35 USC Section 102(a) have been withdrawn. Claim 38 has been cancelled and new claims 39 and 40 are added. Support for new claim 39 is found, for example, in the published application at paragraphs [0047], [0048], and [0066]. Support for new claim 40 is found, for example, in the published application at paragraphs [0041] and [0066]. No new matter is added by these amendments. All citations herein to paragraph numbers refer to the published Application No. US 2007/0092489.

Claim 33 stands rejected under 35 USC Section 112 as indefinite. Claim 33 has been corrected to overcome this rejection. Applicants therefore request that the rejection of claim 33 for indefiniteness be withdrawn.

Claims 1, 3, 8, 10, 33, and 38 stand rejected under 35 USC 102(b) as anticipated by Halbreich (US 6,150,181). Claim 38 is cancelled and therefore this rejection is moot with respect to claim 38. The Office Action states that Halbreich teaches nanoparticles composed of magnetite  $\text{Fe}_3\text{O}_5$  and maghemite  $\gamma\text{Fe}_2\text{O}_3$ , and that these compounds can be reasonably interpreted to be "metals," but the Office Action provides no evidentiary support for this interpretation.

Applicants traverse this rejection. The American Heritage Science Dictionary defines "metals" as follows:

(1) Any of a large group of chemical elements, including iron, gold, copper, lead, and magnesium, that readily become **cations** and form **ionic bonds**, having relatively free **valence electrons** (electrons in the outer shells). Metals are generally good conductors of electricity because of the freedom of their valence electrons. Metals generally conduct heat well, and in solid form are relatively malleable and ductile compared to other solids. They are usually shiny and opaque. All metals except mercury are solid at room temperature.

(2) An alloy, such as steel or bronze, made of two or more metals.

[http://dictionary.reference.com/browse/metals#dict\\_header](http://dictionary.reference.com/browse/metals#dict_header).

The Advisory Action states, "A composition comprising a metal' recited in claim 1 encompasses the iron present in iron oxide. It is noted that the specification does not provide

any particular definition for the word 'metal' and the open language 'comprising' recited in claim 1 certainly indicate the possibility of the presence of components other than a pure metal element...."

Metal oxide compounds such as magnetite and maghemite are not "metals" as that term is used by those of ordinary skill in the art, and as evidenced by the dictionary definition above. The definition of "metal" proposed by the Office Action would include materials such as NaCl that are outside the broadest reasonable interpretation of the term "metal". Applicants again request that the Examiner provide an affidavit or declaration to support Official Notice that the term "metal," as used and understood by persons of ordinary skill in the art, includes metal oxide compounds, including citation to some authority to provide sound technical reasoning for the assertion, as required by MPEP Section 2144.03(C). ("If Applicant challenges a factual assertion as not properly officially noticed or not properly based upon common knowledge, the examiner must support the finding with adequate evidence. If the examiner is relying on personal knowledge to support the finding of what is known in the art, the examiner must provide an affidavit or declaration setting forth specific factual statements and explanation to support the finding." MPEP Section 2114.03(C)).

Claims 1, 8-10, 33, and 38 stand rejected under 35 USC Section 102(b) as anticipated by Feijen (US 4,634,762). Claim 38 is cancelled and therefore this rejection is moot with respect to claim 38. The Office Action states that Feijen teaches covalently bonded conjugates of an anticoagulant and protein which are coupled via amide linkages. Office Action, page 7. Applicants traverse this rejection for the following reasons.

The Advisory Action states, "Furthermore, Feijen *et al.* teaches conjugates for *coating* a surface of a medical device and the conjugates are covalently bonded conjugates of an anticoagulant and protein that are prepared in the presence of a coupling agent that forms amide linkages between the anticoagulant and the protein." (Italics added.)

As explained in this quote from the Advisory Action, Feijen teaches covalent bonding of heparin to a protein, but Feijen does not teach *covalent bonding* of heparin or a protein, or the heparin-protein complex *to a metal surface*. Feijen, in contrast, teaches *coating a surface by adsorbing* the heparin-protein complex to the surface (col.3, lines 46-55). In col. 4, lines 20-24, Feijen states, "Adsorbed conjugates will exhibit desorption to the extent that the conjugates

will become generally released ...." Applicants' claims are directed to the covalent bonding of a modified protein to a metal surface, as discussed further below, and are not directed to coating a surface with a protein complex. Applicants' covalently-bound modified protein does not "desorb" from the surface, in the manner of Feijen's heparin-protein conjugate, because it is *covalently bound* to the metal surface, not just coated onto the surface. Therefore, Feijen does not disclose every limitation of Applicants' claims and cannot anticipate claims 1, 8-10, or 33. Accordingly, Applicants request that the rejection of these claims over Feijen under Section 102(b) be withdrawn.

The Office Action states that Feijen also teaches that conjugates of an anticoagulant and a protein may be used with "a surgical apparatus (which inherently reads on the metal surface of a medical device recited in claim 8)," (Office Action, p. 7). The Office Action rejects claims 8-10 for this reason. Applicants traverse this rejection for the reasons stated below.

"To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" MPEP Section 2112 IV quoting *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted). "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP Section 2131 quoting *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

A metal surface is not "necessarily present" in the term "surgical apparatus," as the surgical apparatus may also be composed of nonmetals such as plastics, teflon, fibers, etc. Feijen does not state that the "surgical apparatus" is comprised of metal or suggest what material his disclosed surgical apparatus comprises. For this reason, a metal surface is not inherent in the term "surgical apparatus."

The Advisory Action states that "Feijen et al. teaches extra-corporeal medical device includes a catheter (which is encompassed by claims 1,8-9 of instant application) .... Applicant does not provide any evidence that the catheter taught by Feijen is structurally different [than] the catheter recited in claim 9 of the instant application."

Claims 8 and 9 of the application require that the catheter comprises a metal surface. Nothing in Feijen suggests that the disclosed catheter has a metal surface in whole or in part. Feijen does not teach the limitation of a metal surface explicitly or inherently. Feijen states that a "material surface" (col. 8, line 47) may be coated with heparin or a heparin-protein conjugate. Feijen also discusses the use of heparin conjugates with "extracorporeal devices such as catheters ... prosthetic devices ... artificial blood vessels ... surgical apparatus such as oxygenators" at col. 4, lines 27-31. In the Abstract, Feijen states "these conjugates are useful for enhancing the blood compatibility of certain surfaces of a prosthetic device, a surgical apparatus, or an extra-corporeal medical device." None of these statements discloses a metal surface. Accordingly, Feijen does not disclose every limitation of claims 8-10, either explicitly or inherently, and cannot not anticipate these claims. Therefore, Applicants request that the rejection of these claims over Feijen under Section 102(b) be withdrawn.

Claims 1, 8-10, 33 and 38 stand rejected under 35 USC 102(e) as anticipated by Kutryk (US 7,037,332). Claim 38 is cancelled and therefore this rejection is moot with respect to claim 38. The Office Action states that Kutryk discloses a medical device *coated* with antibodies and a layer of matrix, wherein the antibodies are covalently attached to the matrix and the matrix may be covalently attached to the device. Applicants traverse this rejection for the following reasons.

However, the antibodies taught by Kutryk are not covalently bound to a metal surface directly or indirectly. The antibodies are cross-linked to a matrix which forms a "coating" on the surface. (Kutryk Abstract, col. 12, lines 15-23). The matrix is "*coated*" onto the medical device as described in Kutryk, column 10, lines 15-29, as follows: "The stent is dipped or sprayed with a liquid solution of the matrix of moderate viscosity." Col.10, lines 24-26.

In Applicants' claims, "the modified protein is covalently bound to the surface." (paragraph [0016]). The Office Action states that "the limitation 'modified protein is covalently bound to the metal surface' recited in claim 1 does not require the amino acid residue of the modified protein directly forms a covalent bond in the absence of a cross-linker/coupling agent." (Office Action, page 11). However, this interpretation is not correct. Instead, the surface of the metal device is modified with a surface modifier that chemically coordinates, *i.e.*, is covalently linked, with the metal surface. (Paragraphs [0041] - [0044], [0066]). As shown in Figure 1B, the surface is then reacted with a compound such as SPDP to create reactive groups on the surface modifier. These reactive groups covalently bind to the modified protein. Thus, unlike

the invention of Kutryk, the modified protein is covalently bound to the reactive groups of the surface modifier, which is chemically coordinated, *i.e.*, covalently bound, with the metal surface. Neither the surface modifier nor the protein is a "coating." Therefore, the modified protein is directly "covalently bound to the metal surface."

An exemplary embodiment, described in paragraphs [0047] - [0048] as follows, makes this clear.

[0047] For example, the metal surface can be treated with either polyallylaminobisphosphonate (PAABP) or poly-bis-phosphonates containing latent thiol groups to form a chemisorption layer with binding through coordination of the bisphosphonate groups. The primary amino groups of the PAABP chemisorption layer can be transformed with SPDP into the thiol-reactive pyridyldithio groups, which then can be used for the immobilization of thiol-containing proteins.

[0048] The chemisorption layers of poly-bisphosphonates with latent thiol groups can be reduced with tris (2-carboxy-ethyl)phosphine (TCEP) in aqueous buffered solutions, at pH ca. 5, for several minutes at room temperature. The immobilized thiol groups thus formed can then be reacted with thiol-reactive groups such as pyridyldithio or maleimido which have been preintroduced into proteins by standard methods known in the art.

For these reasons, Kutryk does not disclose a composition comprising a metal surface and a modified protein, wherein the modified protein is covalently bound to the metal surface. Therefore, Kutryk does not anticipate claims 1, 8-10, or 33. Applicants respectfully request that the Section 102(b) and (e) rejections of claims 1, 8-10, and 33 be withdrawn.

Claims 1, 3, and 34 stand rejected under 35 USC Section 103(a) as unpatentable over Kutryk in view of Xu (US 7,001,745). Applicants traverse this rejection for the following reasons. As discussed above, Kutryk does not disclose a composition comprising a metal surface and a modified protein, wherein the modified protein is covalently bound to the metal surface. As stated in the Office Action, Xu discloses intein-mediated peptide ligation to generate a fusion protein. However, Xu does not disclose a composition comprising a metal surface and a modified protein, wherein the modified protein is covalently bound to the metal

surface. Because Xu cannot compensate for the elements missing in Kutryk, neither Xu nor Kutryk, alone or in combination, renders claims 1, 3, or 34 unpatentable.

Claims 1, 33, and 35-37 stand rejected under 35 USC Section 103(a) as unpatentable over Kutryk in view of Li (US 6,524,572). Applicants traverse this rejection for the following reasons. As discussed above, Kutryk does not disclose a composition comprising a metal surface and a modified protein, wherein the modified protein is covalently bound to the metal surface. The Office Action states that Li discloses a fusion protein comprising the extracellular domain of CAR/Hinge/protein A ligand for protein targeting. However, Li does not disclose a composition comprising a metal surface and a modified protein, wherein the modified protein is covalently bound to the metal surface. Because Li cannot compensate for the elements missing in Kutryk, Li and Kutryk, alone or in combination, do not render claims 1, 3, or 34 obvious.

### Conclusion

For these reasons, it is respectfully submitted that the claims are in condition for immediate allowance and a notice to this effect is solicited. The Examiner is invited to telephone Applicants' attorney if it is believed that a telephonic interview would expedite prosecution of the application.

Respectfully submitted,



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